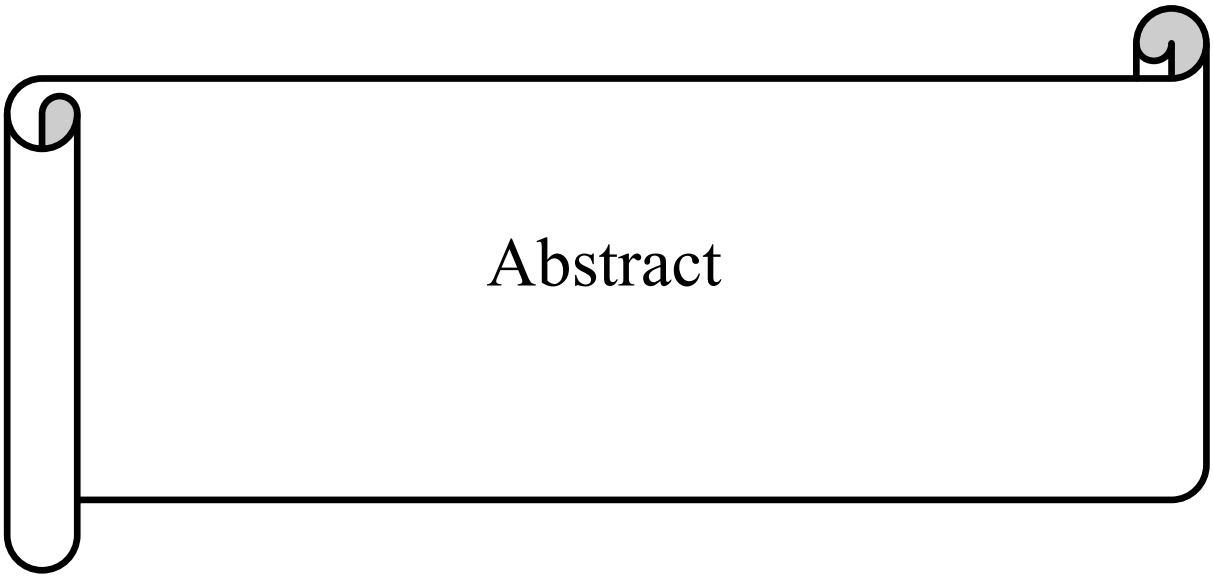

Abstract

ABSTRACT

The thesis entitled **"*Synthesis and Biological Evaluation of Benzo[4,5]thiazolo[1,2-a]pyrimidine and 1, 2, 3-Triazole heterocycles as Anticancer agents*"** has been divided into four chapters.

CHAPTER I: General Introduction: Micro review on Benzothiazolopyrimidine and 1,2,3- Triazole

CHAPTER II:

Section-A : Synthesis of novel benzo[4,5]thiazolo[1,2-*a*]pyrimidine-3-carboxylate derivatives and biological evaluation as potential anticancer agents

Section-B: Synthesis and anti cancer activity of benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carbonyl)piperazine-1-carbodithioate derivatives

CHAPTER III:

Section-A: Synthesis of novel 1,2,3-triazole substituted chalcone acetamide derivatives as potential antitumor agents

Section-B: Synthesis and evaluation of anti proliferative activity of novel 1,2,3-triazole substituted pyrazole derivatives

CHAPTER IV: Design and Synthesis of 1,2,3-triazole substituted benzo[*d*] imidazole and 1,2,3-triazole substituted quinazolin-4(3*H*)-one derivatives as potential anti proliferative agents

Chapter I:

General Introduction

Benzo[4,5]thiazolo[1,2-*a*]pyrimidines:

Pyrimidines have a long distinguished history extending from the days of their discovery as important constituents of nucleic acids to their current use in the chemotherapy of AIDS. The pyrimidine ring is found in vitamins like thiamine, riboflavin and folic acid. During the last two decades, several pyrimidine derivatives have been developed as chemotherapeutic agents and have found wide clinical applications. Benzothiazoles represent a class of heterocyclic compounds of great importance in biological chemistry. They exist in many condensed fused systems that were found to possess a wide range of activity. Various literature reports display numerous fused pyrimidine ring systems and their chemotherapeutic activities as anticancer, antibacterial and antiviral agents. Since the two heterocyclic moieties, benzothiazoles and pyrimidines, constitute two active pharmacophores that are highly active against antitumour and antimicrobial, combining the two is expected to have a synergistic effect on their biological properties. Also substituted thiazolopyrimidine ring systems were reported to possess antitumour activity. The reported significance of such synthons generated the interest to exploit this valuable structure in the designing and the synthesis of new benzo [4,5]thiazolo[1,2-a]pyrimidine-3-carboxylate derivatives.

1,2,3-Triazoles:

The chemistry of heterocyclic compounds continues to be an exploring field in the organic and pharmaceutical chemistry. 1, 2, 3-Triazoles constitute an important class of nitrogen heterocycles in the field of organic and medicinal chemistry. Medicinally, they have been shown to possess a wide range of diverse interesting pharmacological properties such as antituberculosis, anti-HIV, antimalarial, antiepileptic, antiallergic, antileishmanial, antifungal, anticancer and antibacterial activities. In addition, these molecules have been utilized as proton transport facilitators, glycoside cluster arrays, spacers or linkers to dendrimers, DNA cleaving agents, structural components in hyper

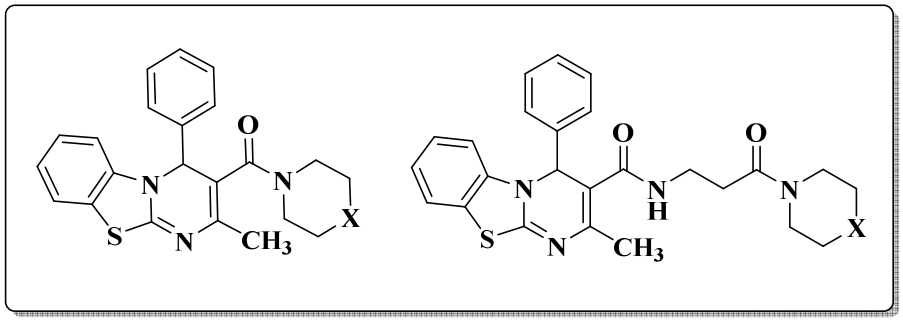
branched polymers and most importantly in liquid crystals. Synthesis of 1,2,3-triazoles is mainly the copper(I) catalyzed 1,2,3-triazole forming reaction between azides and terminal alkynes is called 'click chemistry'. So a programme on structural modification and development a novel building blocks of 1, 2, 3-triazole undertaken in the present work. Since all the products were evaluated for their biological activity, in this context report studies on the synthesis and chemistry of 1, 2, 3-triazole to study their structure activity relationship. Synthesis of novel series of 1,2,3-triazole based building blocks, their biological evaluation of their preliminary cytotoxicity against the human cancer cell lines *in vitro*. During antitumor screening of the structural analogues of the title compounds, we synthesized most of the compounds shown antitumor activity against human cancer cell lines.

Chapter II

Section-A: **Synthesis of novel benzo[4,5]thiazolo[1,2-*a*]pyrimidine-3-carboxylate derivatives and biological evaluation as potential anticancer agents**

In this section we developed a novel benzo[4,5]thiazolo[1,2-*a*]pyrimidine-3-carboxylate derivatives which have anti tumour activity. Analysis of structure-activity relationships identified the benzothiazole and pyrimidine nuclei as being essential for potent activity, and substitution at the carboxylic acid 3'-position of the benzothiazolopyrimidine ring when condensed with methyl piperazine and piperidine moieties increases the cytotoxicity activity against human breast cancer cell lines MDA-MB-231 and MCF-7 more efficiently, when compare to the secondary amines which shows moderate activity with the above cell line *in vitro*. When chain length was increased with the condensation of β-alanine at the third position of benzothiazopyrimidine ring, decreases the cytotoxicity compare to piperidine and methylpiperazine moieties Significantly, (2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo [3,2-*a*]pyrimidin-3-yl)(piperidine-1-yl) methanone and (2-methyl-4-phenyl-4H-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-3-yl)(4-methylpiperazin-1-yl)methanone out per formed their best cytotoxicity activity against breast cancer cell lines.

In another reaction, ethyl-3-(2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxamido)propanoate was obtained in good yield by the condensation of pyrimidine-3- carboxylic acid with β-alanine ethyl ester in the presence of HOBt, EDC.HCl and triethylamine and the compound was confirmed based on appearance of bands at 1642, 1623 cm^{-1} for C=O and ester carbonyl stretching in IR spectrum. The ^{1}H NMR spectra showed the characteristic ester signals at δ1.22 as triplet representing three hydrogens and δ 3.42-3.52 as a multiplet representing for two protons of ester -CH_2. Upon hydrolysing the compound was converted to 3-(2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxamido) propanoic acid using KOH, ethanol at reflux temperature. Treatment of compound acid with piperidine in the presence of HOBt, EDC.HCl and triethylamine at room temperature gave the targeted methyl-N-(3-oxo-3-(piperidin-1-yl)propyl)-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxamide in good yield.

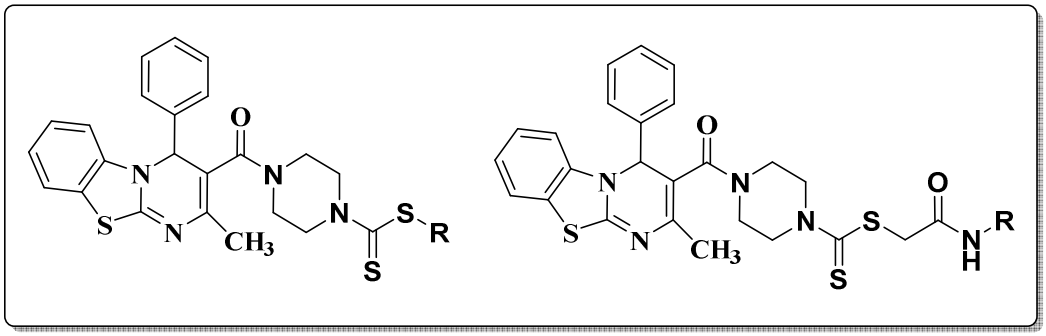


Novel building blocks of benzo[4,5]thiazolo[1,2-*a*] pyrimidine-3-carboxylate

Section-B: Synthesis and anti cancer activity of benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carbonyl)piperazine-1-carbodithioate derivatives

In this topic, we developed a novel benzo[4,5]thiazolo[1,2-a]pyrimidine-3-carbonyl piperazine carbodithioate derivatives. The key intermediate used for the synthesis of final compounds of both the series was 2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylic acid, which in turn was prepared by one-pot condensation of 2-aminobenzothiazole with substituted benzaldehyde and ethyl acetoacetate in the presence of ethylene glycol by catalysing with TBAHS to give compound which was

hydrolyzed using KOH, ethanol refluxed to get the targeted compound, 2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylic acid in quantitative yield. Treatment of pyrimidine-3-carboxylic acid with 1-BOC piperazine in the presence of HOBt, EDC.HCl and triethylamine at room temperature gave the tert-butyl 4-(2-methyl-4-phenyl-4H-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carbonyl)piperazine-1-carboxylate which was treated with trifluoro acetic acid in dichloromethane will give the compound (2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-3-yl)(piperazin-1-yl)methanone in good yield. In another reaction, the compound (2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-3-yl)(piperazin-1-yl)methanone treated with 2-bromo-N-phenylacetamides in the presence of carbondisulfide by using base potassium phosphate in acetone will yield the targeted benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carbonyl)piperazine-1-carbodithioate derivatives in good to excellent yields.



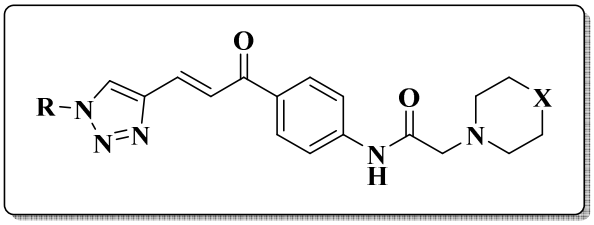
Novel benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carbonyl)piperazine-1-carbodithioate derivatives

Chapter-III

Section-A: Synthesis of novel 1, 2, 3-triazole substituted chalcone acetamide derivatives as potential anti tumor agents

Synthesis of novel 1, 2, 3-triazole substituted chalcone acetamide derivatives is accomplished starting from 1-substituted 1,2,3-triazol-4-yl-methanol. The 1-substituted -1, 2, 3-triazol-4-yl-methanol was oxidized to corresponding aldehyde by using Jones reagent followed by the reaction with 4-aminoacetophenone in ethanol by using sodium

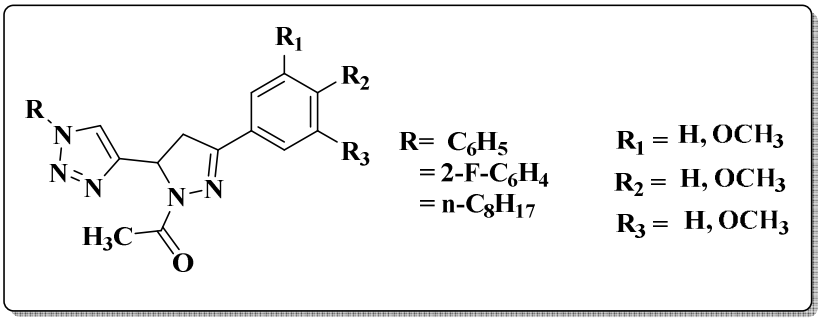
hydroxide as base at room temperature furnished amino chalcone derivative. The (*E*)-1-(4-aminophenyl)-3-(1-substituted-1*H*-1, 2, 3-triazol-4-yl) prop-2-en-1-one was reacted with bromoacetyl bromide in dichloromethane in presence of potassium carbonate at 0^{o}C to RT will get the corresponding 1, 2, 3-triazole substituted chalcone bromo acetamide derivatives which was treated with piperazine like compounds in the presence of acetonitrile by using triethylamine as base will get the targeted 1,2,3-triazole substituted chalcone acetamide derivatives.



Novel 1, 2, 3-triazole substituted chalcone acetamide derivatives

Section-B: Synthesis and evaluation of anti proliferative activity of novel 1, 2, 3-triazole substituted pyrazole derivatives

In our present work, we developed a series of 1 ,2, 3-triazole substituted pyrazole derivatives as potent anti cancer agents. The key intermediate used for the synthesis of final compounds was The 1,4- substituted triazole aldehydes which in turn prepared by oxidation of triazole alcohol with jones reagent. The compound which on further reacted with substituted acetophenones in the presence of 10% sodium hydroxide in ethanol will give corresponding triazole chalcones which on treated with hydrazine hydrate in acetic acid at 80 ^{o}C will give the desired compounds obtained in good yields.

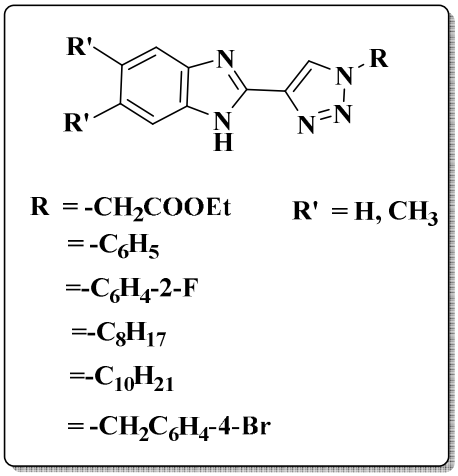


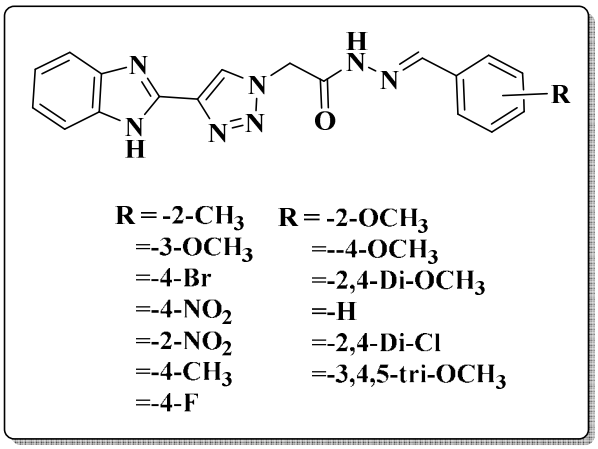
Novel 1, 2, 3-triazole substituted pyrazole derivatives

CHAPTER IV: Design and Synthesis of 1, 2, 3-triazole substituted benzo[*d*]imidazole and 1,2,3-triazole substituted quinazolin-4(3*H*)-one derivatives as potential anti proliferative agents

The synthesis of triazole substituted benzimidazole derivatives can be obtained by the reaction sequence, the propargyl alcohol on reaction with various alkyl azides under Sharpless conditions through click chemistry concept gave exclusively 1,4-disubstituted 1,2,3-triazole alcohols and then oxidized to aldehydes followed by reaction with phenylene diamines resulted 1, 2, 3-triazole substituted benzo[*d*]imidazole.

In another scheme, the propargyl alcohol on reaction with ethyl 2-azidoacetate under Sharpless conditions through click chemistry concept gave exclusively 1,4-disubstituted 1,2,3-triazole which on oxidized to give ester of triazole aldehyde. The aldehyde was further reacted with phenylene diamine resulted 1, 2, 3-triazole substituted benzo[*d*]imidazole ester which on further treated with hydrazine hydrate gave the hydrazide compound. The compound hydrazide was further reacted with various aldehydes obtained (*E*)-N'-(substituted benzylidene)-2-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)-1*H*-1,2,3-triazol-1-yl)acetohydrazides.



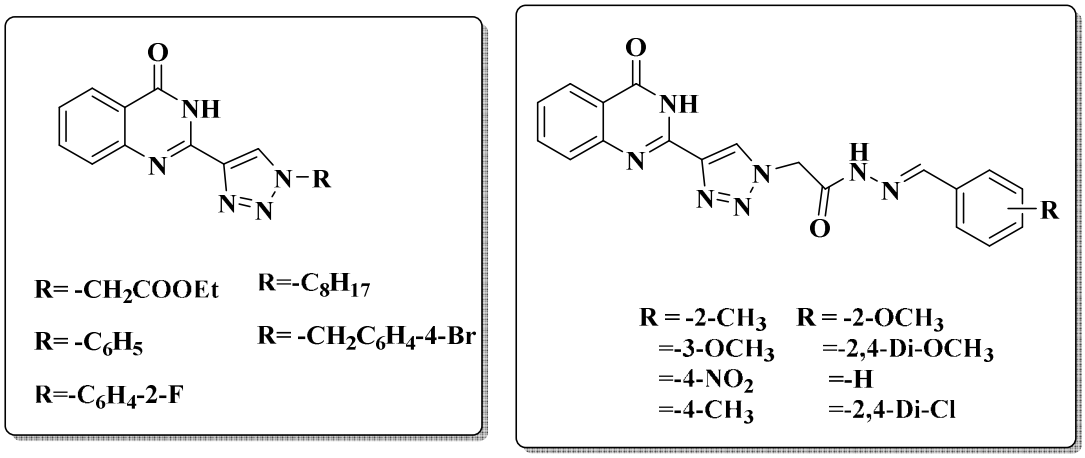


Novel 1, 2, 3-triazole substituted benzo[*d*]imidazole derivatives

Quinazolinones:

The synthesis of triazole substituted quinazolin-4(3*H*)-one derivatives can be obtained by the reaction sequence, the propargyl alcohol on reaction with various alkyl azides under Sharpless conditions through click chemistry concept gave exclusively 1,4-disubstituted 1,2,3-triazole alcohols. The compounds were oxidized to aldehydes followed by reaction with anthranilamide resulted quinazolinone derivatives.

In another scheme, the propargyl alcohol on reaction with ethyl 2-azidoacetate under Sharpless conditions through click chemistry concept gave exclusively 1,4-disubstituted 1,2,3-triazole which on oxidized to give aldehyde. The aldehyde was further reacted with anthranilamide resulted quinazoline triazole ester which on further treated with hydrazine hydrate gave the hydrazide compound. The compound hydrazide was further reacted with various aldehydes obtained (*E*)-N'-(substituted benzylidene)-2-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)-1*H*-1,2,3-triazol-1-yl)acetohydrazides. The structures of all the synthesized compounds were confirmed by spectral data.



Novel 1,2,3-triazole substituted quinazolin-4(3*H*)-one derivatives